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EDITORIAL COMMENT

Subclinical Cardiotoxicity Associated With Cancer Therapy

Early Detection and Future Directions*

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Advances in cancer treatment have reduced cancer-related mortality, adding to the ranks of cancer survivors (1). Unfortunately, chemotherapy and radiation often cause acute or chronic cardiovascular complications, which are the major causes of noncancer mortality among survivors. Compared with siblings, cancer survivors are 10 times more likely to develop coronary disease and 15 times more likely to develop heart failure (HF) (2). Thus, screening for cardiovascular complications has been advocated for patients who have received anthracycline and/or radiation. In this issue of the *Journal*, Armstrong et al. (3) report a cross-sectional

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analysis of cardiac function in long-term childhood cancer survivors from a single center using transthoracic echocardiography to assess myocardial strain imaging and diastolic function. SJLIFE (St. Jude Lifetime Cohort Study) analyzed 1,807 childhood survivors who were diagnosed with cancer more than 10 years previously and received either anthracycline or chest radiotherapy or both. Systolic dysfunction, defined as left ventricular (LV) ejection fraction (LVEF) < 50%, was detected in only 5.8% of survivors. Among patients with preserved LV function, 28% and 8.7% were found to have abnormal global longitudinal strain (GLS) and diastolic dysfunction, respectively. These findings were consistent with those of previous studies, which demonstrated that asymptomatic cancer survivors have subtle abnormalities of both systolic and diastolic function compared with the normal population (4). A recent meta-analysis suggested that GLS might have prognostic value for the development of cardiotoxicity; however, this was on the basis of results from 8 studies with <500 patients, with most of these studies having only 1 year of follow-up (4). Moreover, the definition of cardiotoxicity was ambiguous, and the majority of patients had LVEFs within the normal range (4). It should be noted that abnormal GLS is defined as more than 2 SDs above the mean using sex-specific, age-specific, and vendor-specific strain values identified in a normative Japanese study (5). However, the SJLIFE population is 84% white. The correlation between the incidence of HF and the cumulative dose of anthracycline and radiation is well established in the published research (6). The investigators also demonstrate a dose-response relationship between the cumulative anthracycline or radiation dose and the development of GLS abnormalities. This study therefore confirms the limitation of current standard screening with ejection fraction and highlights the value of strain imaging.

Anthracycline exerts deleterious effects on cardiomyocytes, endothelial cells, fibroblasts, and cardiac stem cells. It inhibits topoisomerase II (Top2), an essential enzyme for unwinding deoxyribonucleic acid strands during deoxyribonucleic acid replication or transcription (7). Anthracycline targets Top2β, the primary Top2 isoform in the heart, triggering profound changes in the transcriptome that lead to defective mitochondrial biogenesis and reduced antioxidative enzymes, manifested as increased production of reactive oxygen species and cardiomyocyte death (8). Anthracycline has also been shown to reduce coronary branching, capillary density, and the expression of myocardial vascular

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endothelial growth factor (9). The number of cardiac progenitor cells and their ability to differentiate into endothelial cells, smooth muscle cells, or myocytes is also diminished (9). Thus, the ability of the heart to adapt to stress is impaired after exposure to anthracycline.

A wide range of cardiovascular problems can also arise from chest radiation therapy (10). Experimental evidence suggests that endothelial cells are the major cardiovascular targets of radiation. Mature cardiac myocytes are terminally differentiated cells and are, therefore, less sensitive to radiation compared with endothelial cells. Radiation causes microvascular and macrovascular damage, the underlying pathophysiology of radiation-induced heart disease. Pathological features of radiation-induced macrovascular change include adventitial scarring, medial atrophy, intimal atherosclerosis with necrosis, and fibrocalcification (10). Disruption of the microvasculature causes local ischemic injury and an inflammatory response, which triggers the fibroblast proliferation and an increase in the collagen content of the heart. These pathological changes may not lead to a reduction in LVEF but can be detected by a more sensitive technique, such as GLS.

According to the American College of Cardiology and American Heart Association guidelines, patients who received cardiotoxic agents were considered at risk for developing HF or stage A HF (11). Periodic LVEF screening has been advocated for this vulnerable population (12). If LV dysfunction is detected, HF treatment is often initiated promptly. Even with aggressive medical management, many cancer survivors went on to develop stage D HF, which eventually required heart transplantation (13). To prevent further deterioration of LV function, oncocardiologists have used advanced cardiac imaging and/or biomarkers to detect LV dysfunction early (4). Although SJLIFE is the largest study to date using GLS to detect late cardiotoxicity in cancer survivors, it provides only a snapshot of the population at risk, without long-term outcomes.

Even though we can detect subclinical changes of LV function, the benefit of early detection is still unknown. A limited number of studies have evaluated the benefit of early intervention in asymptomatic patients with subclinical LV dysfunction, with contradictory results (14,15). A screening test is considered cost efficient only if early detection will lead to intervention that improves outcomes. The investigators have a unique opportunity to use the SJLIFE cohort to evaluate whether early intervention could prevent or slow the progression of subclinical LV dysfunction (assuming that subclinical LV dysfunction will progress to clinical HF with time). There is currently no proven treatment that will reverse cardiac injury that was already incurred after cancer treatment. It would be more desirable to prevent cardiovascular damage with primary prevention. Advances in radiation technology have improved the ability to deliver safe radiation doses to primary tumors while sparing normal tissues (16). Primary prevention for anthracycline-induced cardiotoxicity is also clinically feasible, albeit rarely practiced (17).

There is no question that a substantial number of pediatric cancer survivors have evidence for subclinical LV dysfunction. Future studies are required to examine the progression of subclinical LV dysfunction to clinical cardiomyopathy and to determine whether early intervention in these patients will lead to improvements in long-term clinical outcomes.

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